Remarks

I. A. Advisory Action.

Applicants respectfully traversed the Examiner's refusal to enter the amendment submitted after final. Applicants submit the amendment required no further search. In addition, to the extent a placed claims 94, 115, 118, and 120, per the Examiner's indication of allowable subject matter, the amendment should have been entered in part. Furthermore, the Examiner's assertion that the amendment to claim 96 raised new issues, because the amendment requires the "functional regulatory regions that must now be between newly prescribed limits of 15 to 250" nucleotides fails to consider both the teachings of the disclosure and the previous amendment to claim 97 presented in the response of May 27, 2003.

B. Claim Objections

Applicants thank the Examiner for the indication of allowable subject matter in claims 94, 115, 118, and 120, and have presented these claims as independent claims amended to conform to the indication of allowable subject matter. Applicants solicit an indication that the claims are in allowable form in the subsequent Office Action.

II. Rejection of Claims 79-81, 91, 96, 97, 100, 102, 103, 106, 108, 109, 112, 114, 121, 124, and 126 under 35 U.S.C. § 112 first paragraph

Claims 79-81, 91, 96, 97, 100, 102, 103, 106, 108, 109, 112, 114, 121, 124, and 126 stand rejected under 35 U.S.C. § 112 first paragraph for allegedly failing to comply with the written description requirement. The Examiner has maintained the outstanding written description rejection alleging Applicants' arguments are not persuasive because "the specification must provide some link between structure and function under the guidelines of 35 U.S.C. 101, which applicants have disclosed as fragments retaining translational control activity

over the subject TIGR protein."[1] The Examiner asserts that what is at issue is "whether adequate description exists for fragments that retain the correlated activity." The Examiner alleges that "fragments of 15 to 250 nucleotides that are expected to retain translational control over said [TIGR] protein have not been sufficiently described in the specification."[2] In addition, the Examiner alleges that there is a failure of the specification to provide some link between structure and function of the fragments retaining translational control activity over the subject TIGR protein.[3] In the Advisory Action, the Examiner further asserts that applicants disclosure of some regulatory elements is insufficient to support or possession of the genus claimed.

Applicants maintain that the Examiner has failed to apply proper standards for determining the adequacy of written description, which is essentially a fact-based inquiry. *See Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) and *In re DiLeon*, 436 F.2d 1404,1405 (C.C.PA. 1971)). Instead, the Examiner bases his assertion of unpatentability under 35 USC 112 first paragraph on erroneous premises, including the premise that fragments of the disclose nucleotide sequence "are expected to retain some translational control over the expression of

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[1] Applicants note that the Examiner has improperly relied upon 35 U.S.C. § 101 in constructing the rejection under § 112, first paragraph written description, based upon the "written description guidelines," which are neither statute, nor substantive rules. The utility requirement of 35 U.S.C. § 101 and the written description requirement of § 112 first paragraph are separate and distinct statutory requirements. While Applicants maintain that the Examiner's reliance on 35 U.S.C. § 101 is improper, they also maintain that their disclosed use in diagnostic assays to detect polymorphisms or mutations associated with diagnosis and prognosis of glaucoma and ocular hypertensive disorders is more than sufficient to meet the utility requirement of 35 U.S.C. § 101. *See e.g., Nelson v. Bowler 626 F.2d 853 (CCPA 1980).* In addition, as the Examiner inappropriately changed the scope and nature of the rejection by interjecting a new statutory basis of rejection without issuing a new first action on merits, and as such the finality of the previous Office Action was improper and should have been withdrawn.

[2] Office Action dated August 13, 2003 at page 4.

[3] Office Action dated August 13, 2003 at page 4.

said [TIGR] protein," and the premise that Appellants have not indicated, any regulatory function for fragments of the disclosed in nucleotide sequence.

Appellants also maintain that disclosure of "such descriptive means as words, structures, figures, diagrams formulas, etc., that fully set forth the claimed invention" satisfies the written description requirement, and that they have met this burden. *Enzo Biochem*, 296 F.3d at 1329 (quoting from *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). Appellants maintain that they have adequately met the written description requirement for genetic material, which "requires a precise definition, such as by structure, formula, chemical name, or physical properties" by providing the sequence of the claimed nucleic acids. *See, Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir. 1993)). Appellants note that the disclosure of the specific nucleotide sequence of SEQ ID NO.: 3 not only provides chemical formula information, but also provides the structure of the claimed molecules.

Applicants submit they described the claimed fragments of SEQ ID NO.: 3 by supplying the sequence of SEQ ID NO.: 3, and fragments from about 15 to about 250 nucleotides of SEQ ID NO.: 3,[4] which itself is sufficient to meet the written description requirement. In addition, Applicants submit the Examiner's acknowledgement that the disclosure adequately sets forth SEQ ID NO.: 3, and that it is possible to envision fragments of SEQ ID NO.: 3 [from 15 to 250 nucleotides] is in direct conflict with the Examiner's position.[5]

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[4] See the disclosure at page 28, lines 1-8.

[5] See the Office Action dated August 13, 2003 at page 4, lines 8-19.

In direct contrast to the Examiner's assertion regarding the adequacy of the specification, Applicants submit, the disclosure adequately discloses the claimed invention. With regard to functional regulatory elements, disclosure at page 27 states:

> A functional regulatory region of the TIGR gene may be a TIGR promoter sequence. ... A number and of regulatory elements are discussed below, and the equivalent of those activities can represent the functional regulatory region of the TIGR gene.

A functional regulatory region, as defined, does not need to be a complete and functional promoter that retains "translational control activity to the expression of said [TIGR] protein." Rather, a functional regulatory region encompasses one or more *cis* regulatory regions within the promoter. The disclosure sets forth a substantial number of *cis* regulatory elements within SEQ ID NO.: 3, supporting the claimed genus.[6] Moreover, the disclosure sets forth sufficient information for the skilled artisan to identify functional regulatory elements within the claimed sequence through variety of techniques.[7]

It is not the case, as contended by the Examiner, that fragments of the TIGR promoter "have only been described in terms of their function (of modulating translation), along with a method of obtaining (from the 6000 nucleotide SEQ ID NO:3)," and that "although it is possible to envision fragments of SEQ ID NO: 3 as alleged by applicants,

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[6] At pages 25-35 the disclosure sets forth no less then 32 *cis* regulatory elements that appear over 44 time in the 5'untranscribed region of the TIGR gene (see figures 1A – 1E) .

[7] Applicants submit that a skill artisan would know how to identify cis elements within a promoter through the use of one or more techniques, including but not limited to footprint analysis, construction of reporter constructs with different length promoter regions cloned 5' to the reporter region, deletion of promoter sequences, gel retardation analysis. See for example US 6,100,035 *Method of Identifying Cis Acting Nuleic Acid Elements*; Tulchinsky *et al.*, *Transcriptional analysis of the mts1 gene with specific reference to 5'-flanking structures,* PNAS 89:9146-50 (1992); Buckingham *et al.*, *Nucleotide sequence and promoter analysis of Spo13, a meiosis specific gene of Saccharomyces Cerevisiae,* PNAS 87:9406-9410 (1990); Lang *et al.*, *Transcriptional regulation of the human c-myc gene*, Br. J. Cancer Suppl. (1988) 9:62-66 (abstract only); von Beroldingen *et al.*, *Eurkaryotic transcription complexes*, Mol Cell. Biochem. (1984) 62(2): 97-108 (abstract only).

it is not possible to envision such fragments having the broadly claimed function of 'regulatory activity'."[8] The disclosure provides more than a disclosure by function when it sets forth the sequence SEQ ID NO.: 3, which the Examiner admits is adequately disclosed, and a substantial number of *cis* elements within SEQ ID NO.:3. Thus, in contrast to the Examiner's assertions, the disclosure provides more than sufficient information and guidance for a skilled artisan to recognize functional regulatory elements and to "provide some link between structure and function under the guidelines of 35 U.S.C. § 101."[9] In addition, a skilled artisan would be able to identify functional regulatory elements within the claimed sequences through a variety of techniques.[10] In view of the foregoing, the specification provides more than a sequence described by function and a method of obtaining such a sequence.

As with the assertions discussed above, the Examiner's further reliance on MPEP § 2163 to support the assertion that "biomolecule sequences described only by functional characteristics without any known or disclose correlation between that function and the structure of the sequence normally is not sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence," is similarly misplaced. Applicants respectfully submit that a MPEP § 2163 is directed to biomolecules described "only by functional characteristics," whereas Applicants have provided sequence data that forms the basis of the claimed regulatory elements, and therefore do not rely

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[8] *See,* the Office Action dated August 13, 2003, at p. 4.

[9] Applicants maintain that there is no statutory basis for imposing this requirement on patentability. *See* n. 3 *supra.*

[10] *See*, n. 8, *supra.*

on a description based "only on functional characteristics." Furthermore, MPEP § 2163 II. A.3 (a), states that identifying characteristics of a biomolecule may include a sequence or a structure. *See*, *Lockwood v. American Airlines,* 107 F.3d 1565, 1572 (Fed .Cir. 1997) (discussing the written description requirement and asserting that it may be satisfied "by such descriptive means as structures or formulas that fully set forth the claimed invention).

Because Applicants have provided sufficient identifying characteristics[11] including "a precise definition, such as by structure [and] formula," Applicants submit that they have met the requirements of 35 U.S.C. § 112 first paragraph[12] and respectfully request reversal of the Examiner's holding of unpatentablilty under 35 U.S.C. § 112.[13]

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[11] Applicants respectfully submit that although not necessary to meet the requirement for written description, the disclosure is replete with a discussion of the *cis* regulatory elements that map to the 5' untranscribed region of the TIGR gene. *See*, n. 7, *supra.*

[12] *See*, *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991); *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993); *Fiddles v. Baird*, 30 U.S.P.Q.2d 1481, 1483 (Fed. Cir. 1993); and *Regents of the University of California v. Eli Lilly & Co.* 119 F.3d 1159 (Fed. Cir. 1997).

[13] Applicants additionally submit that they have provided more than sufficient disclosure to meet the enablement requirement of 35 U.S.C. § 112.

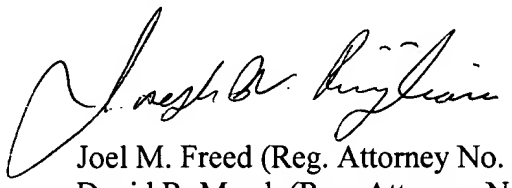
The Recitation of Specific Functional Regulatory Regions Supports the Independent Patentability of Claims 96, 102, 108, 114, and 126

In addition to those reasons for patentability set forth above, Applicants submit that claims 96, 102, 108, 114, and 126, set forth an additional independent basis for patentability under 35 U.S.C. § 112 first paragraph. These claims independently recite specific functional regulatory regions, which are spelled out in the disclosure, and whose positions are expressly taught within the context of SEQ ID NO.: 3. The recitation of specific regulatory region's renders moot the Examiner's arguments that there is insufficient written description of the fragments set forth in the claims, and insufficient guidance for those of skill in the art to select sequences having regulatory activity. Moreover, the recitation of fragments bearing recognize transcription factor binding sites militates against the Examiner's assertion that the claimed fragments are, in and of themselves, expected to retain translational control over the protein. A skilled artisan would recognize that fragments bearing individual *cis* regulatory elements may, or may not, retain sufficient activities to regulate transcription absent the context of other promoter binding elements. Thus, the claimed fragments may contain one or more *cis* regulatory elements (i.e. functional regulatory regions) that may retain some translational control over the TIGR gene when 5' to the transcriptional start site. Fragments, bearing one or a limited number of *cis* regulatory elements, however, may still be employed in the disclosed diagnostic assays, or in the control of gene expression when the fragments are placed in the context of other promoter elements.

Conclusion

Applicants submit that the claims are in condition for allowance and solicit a notice of allowability at the earliest possible time. Should the Examiner have any questions regarding this application, the Examiner is encouraged to contact Applicants' undersigned representative at 202-942-5174.

Respectfully submitted,



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